Impact of Classification of Hilar Cholangiocarcinomas (Klatskin Tumors) on the Incidence of Intra- and Extrahepatic Cholangiocarcinoma in the United States

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Cholangiocarcinomas are topographically categorized as intrahepatic or extrahepatic by the International Classification of Diseases for Oncology (ICD-O). Although hilar cholangiocarcinomas (Klatskin tumors) are extrahepatic cholangiocarcinomas, the second edition of the ICD-O (ICD-O-2) assigned them a histology code 8162/3, Klatskin, which was cross-referenced to intrahepatic cholangiocarcinoma. Recent studies in the United States that included this code (8162/3, Klatskin) with intrahepatic cholangiocarcinoma reported an increasing incidence of intrahepatic cholangiocarcinoma and a decreasing incidence of extrahepatic cholangiocarcinoma. To investigate the impact of this misclassification on site-specific cholangiocarcinoma incidence rates, we calculated annual percent changes (APCs) with data from the Surveillance, Epidemiology, and End Results (SEER) program using a Poisson regression model that was age-adjusted to the year 2000 U.S. population. All statistical tests were two-sided. During 1992–2000, when SEER used ICD-O-2, 1710 intrahepatic cholangiocarcinomas, 1371 extrahepatic cholangiocarcinomas, and 269 hilar cholangiocarcinomas identified by code 8162/3, Klatskin were diagnosed. Ninety-one percent (246 of 269) of the hilar cholangiocarcinomas were incorrectly coded as intrahepatic cholangiocarcinomas, resulting in an overestimation of intrahepatic cholangiocarcinoma incidence by 13% and underestimation of extrahepatic cholangiocarcinomas incidence by 15%. However, even after the exclusion of tumors that were coded to the histology code 8162/3, Klatskin, age-adjusted annual intrahepatic cholangiocarcinoma incidence increased during this period (APC = 4%, 95% confidence interval = 2% to 6%, *P*<.001). [J Natl Cancer Inst 2006; 98:873–5]

Cholangiocarcinomas, primary bile duct cancers, are rare but highly fatal tumors *(1–3)*. Cholangiocarcinomas are classified by the International Classification of Diseases for Oncology (ICD-O) according to their anatomic site (topography) and histology (morphology) *(4)*. Tumors arising from the intrahepatic bile ducts (C22.1; intrahepatic cholangiocarcinomas) are classified as a form of primary liver cancer (C22). In contrast, tumors arising from the extrahepatic bile duct (C24.0; extrahepatic cholangiocarcinomas) are classified as a subset of biliary tract cancers (C24).

Hilar cholangiocarcinomas [also known as Klatskin tumors *(5)*] are anatomically defined as extrahepatic cholangiocarcinomas that involve the hepatic duct bifurcation (Fig. 1). These tumors have distinct clinical and biologic features *(5,6)*. In Version 1 of ICD-O (ICD-O-1, *(7)*), hilar cholangiocarcinomas were not assigned a unique ICD-O code and may have been coded as either intra- or extrahepatic cholangiocarcinomas. In ICD-O-2, hilar cholangiocarcinomas were assigned a unique histology code (8162/3, Klatksin), rather than a topography code, which was cross-referenced to the topography code for intrahepatic rather than extrahepatic cholangiocarcinomas *(8)*. Furthermore, hilar cholangiocarcinomas could also be correctly reported as extrahepatic cholangiocarcinomas using other histology codes. In the year 2000, ICD-O-3 *(4)* cross-referenced hilar cholangiocarcinoma to topography codes for either intrahepatic or extrahepatic cholangiocarcinomas. Thus, hilar cholangiocarcinomas may have mistakenly been classified as intrahepatic cholangiocarcinomas under all versions of ICD-O, although misclassification seems particularly likely under ICD-O-2.

Recent studies in the United States have reported an increasing incidence of primary liver cancer, including intrahepatic cholangiocarcinoma *(9)* and suggest a decreasing incidence of extrahepatic cholangiocarcinoma *(10)*. Given that hilar cholangiocarcinomas are thought to be the most common cholangiocarcinomas *(11)* and were likely misclassified as intrahepatic cholangiocarcinomas under ICD-O-2, cholangiocarcinoma incidence may have been misreported. To investigate this hypothesis, we examined the classification of hilar cholangiocarcinomas reported as code 8162/3 and its impact on intrahepatic and extrahepatic cholangiocarcinoma incidence rates using population-based data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) cancer registry program *(12)*.

Intrahepatic and extrahepatic cholangiocarcinoma incidence rates from nine SEER registries (Atlanta, Connecticut,

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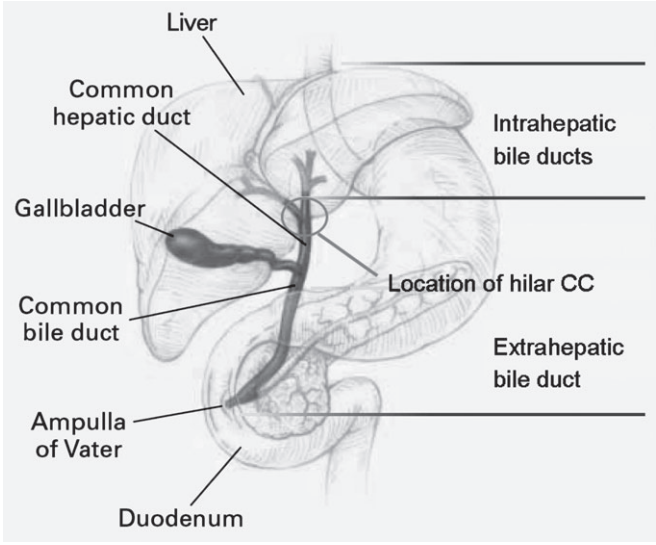

Fig. 1. Anatomic location of hilar cholangiocarcinoma. Adapted with permission from *(18)*.

Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, and Utah) were analyzed for the years 1973–2002. The effect of classification of hilar cholangiocarcinomas reported as code 8162/3 on intrahepatic cholangiocarcinoma and extrahepatic cholangiocarcinoma incidence was analyzed for the years 1992–2000 (ICD-O-2) and 2001–2002 (ICD-O-3).

The identification of intrahepatic and extrahepatic cholangiocarcinomas in SEER was based on the World Health Organization's histologic classification *(13)*. Intrahepatic cholangiocarcinomas were defined by topography code C22.0 (liver) and histology codes 8160 and 8161 or by topography code C22.1 (intrahepatic bile duct) and histology codes 8140, 8160, 8161, 8020, and 8010. Extrahepatic cholangiocarcinomas were defined by topography code C24.0 and histology codes 8010, 8020, 8041, 8070, 8140, 8144, 8160, 8161, 8260, 8310, 8480, 8490, and 8560. Histology code 8162/3, Klatskin was included with extrahepatic cholangiocarcinoma.

Poisson regression was used to assess the effect of year of diagnosis on incidence of intrahepatic and extrahepatic cholangiocarcinomas separately from 1973 to 1991 and 1992 to 2000 to accommodate ICD-O Versions 1 and 2. Data based on ICD-O-3 were available only for the years 2001 and 2002, and, thus, separate analysis of incidence for those years was not feasible. Rates were age-adjusted to the year 2000 U.S. standard population. Relative risks and corresponding annual percent changes (APCs) with 95% confidence intervals (CIs) for the Poisson models were computed (SAS Version 9.1; SAS Institute, Cary, NC). All tests of statistical significance and confidence intervals were two-sided. $P<.05$ was considered statistically significant.

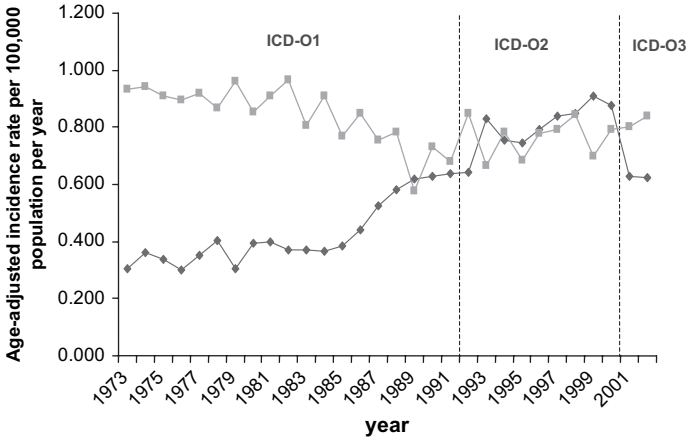

Fig. 2. Age-adjusted incidence rates for intrahepatic cholangiocarcinoma (**diamonds**) and extrahepatic cholangiocarcinoma (including hilar cholangiocarcinomas reported under code 8162/3, **squares**) diagnosed in SEER-9 registries, 1973–2002. ICD-O = International Classification of Diseases for Oncology *(4,7,8)*.

Between 1992 and 2000, 3350 cholangiocarcinomas were diagnosed and reported to SEER, of which 1710 (51%) were intrahepatic cholangiocarcinoma and 1640 were extrahepatic tumors (49%). Of the 1640 extrahepatic tumors, 1371 (84%) were reported as extrahepatic cholangiocarcinoma and 269 (16%) were reported as hilar cholangiocarcinomas under code 8162/3. Ninety-one percent (246 of 269) of the hilar cholangiocarcinomas were reported as intrahepatic cholangiocarcinomas. For the years 2001 and 2002, 54% (22 of 41) of the hilar cholangiocarcinomas reported under code 8162/3 were coded as intrahepatic cholangiocarcinomas.

We calculated the age-adjusted incidence trends for intrahepatic cholangiocarcinoma and extrahepatic cholangiocarcinoma (Fig. 2). Between 1992 and 2000, the incidence of intrahepatic cholangiocarcinoma (excluding hilar cholangiocarcinoma) increased (APC = 4%, 95% CI = 2% to 6%; $P<.001$). The incidence of extrahepatic cholangiocarcinoma (including code 8162/3) remained constant (APC = 1%, 95% CI = −1% to 3%; $P = .33$).

Trends in incidence of hilar cholangiocarcinoma reported under code 8162/3 were similar to the overall incidence trends of extrahepatic cholangiocarcinoma (APC = 1%, 95% CI = −4% to 6%; $P = .6$). Between 1973 and 1991, the increase in incidence of intrahepatic cholangiocarcinoma was similar to that for the time period 1992–2000 (APC = 5%, 95% CI = 4% to 6%; $P<.001$). However, there was a 1% per year decrease in extrahepatic cholangiocarcinoma incidence (APC = −1%, 95% CI = −2% to 0%; $P = .05$).

These data indicate that the current coding of cholangiocarcinomas, particularly hilar cholangiocarcinoma, is problematic for several reasons. It has caused substantial misclassification of extrahepatic as intrahepatic cholangiocarcinomas, which has resulted in overreporting of intrahepatic cholangiocarcinomas by 13% and underreporting of extrahepatic

cholangiocarcinomas by 15%. In addition, there may have been an artificial increase in intrahepatic cholangiocarcinoma rates in 1992 if hilar cholangiocarcinomas were correctly coded as extrahepatic cholangiocarcinoma before the introduction of ICD-O-2. Although false-negative histology or cytology results frequently come from sampling error due to the submucosal growth of these tumors *(14)*, the allocation of hilar cholangiocarcinomas to a histology code rather than a topography code in ICD-O does not allow the histologic definition of these tumors. Because hilar cholangiocarcinomas can be correctly coded as extrahepatic cholangiocarcinomas using several histology codes, it is impossible to identify all hilar cholangiocarcinoma in SEER. This may partly explain the discrepancy between previously reported proportions of hilar cholangiocarcinomas among cholangiocarcinomas in the United States (67%) *(11)* and the proportion of hilar cholangiocarcinomas identifiable in SEER under code 8162/3, Klatskin (8%). Because this frequently cited reference for hilar cholangiocarcinoma incidence *(11)* is a study of patients with histologically confirmed cholangiocarcinomas undergoing surgical exploration at a tertiary medical center, these results may not be generalizable to the U.S. population.

However, even after excluding hilar cholangiocarcinoma from intrahepatic cholangiocarcinoma, the incidence of intrahepatic cholangiocarcinoma did increase statistically significantly over time, with intrahepatic cholangiocarcinomas accounting for more than half of all cholangiocarcinomas recorded between 1992 and 2000. Although there was a slight overall decrease in extrahepatic cholangiocarcinoma incidence between 1973 and 2000, the incidence remained constant between 1992 and 2000.

In summary, the ICD-O-2 coding for hilar cholangiocarcinoma introduced some error in the reporting of cholangiocarcinoma rates in SEER between 1992 and 2000. The validity of our findings also depends, of course, on the completeness and accuracy of the reported registry data. In ICD-O-3, this problem has only partially been addressed by cross-referencing the hilar cholangiocarcinoma histology code 8162/3 to topographies for both intrahepatic and extrahepatic cholangiocarcinoma. We recommend that, in the future, hilar cholangiocarcinoma be assigned a unique topography code listed as a subsite of extrahepatic cholangiocarcinoma, under consideration of other parts of the extrahepatic bile duct. Accurate classification of hilar cholangiocarcinoma would improve the ability to monitor incidence trends of intrahepatic and extrahepatic cholangiocarcinoma and would enhance the ability of studies to examine the etiology of these tumors. In addition, from a clinical and public health perspective, an appropriate, unambiguous coding of hilar cholangiocarcinomas is becoming increasingly more important as more options for therapies, including liver transplantation, are being considered *(15–17)*. The possibility of monitoring and evaluating therapeutic approaches, therapy-related morbidity, mortality, and survival in tumor databases would be greatly enhanced by the addition of a hilar cholangiocarcinoma-specific topography code.

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Notes

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